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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,400	02/27/2004	Peter L. Collins	1173-1061PUS3	5376

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
03/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,400	COLLINS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-61* is/are pending in the application.

4a) Of the above claim(s) *9-14,20-24,27-54,57,60 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,15-19,25,26,55,56,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 12-17-08 has been entered. Claims 6, 8, 15, 18, 19 and 55 have been amended. Claims 1, 3-6 and 8-61 are pending. Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 are under consideration.

Election/Restrictions

1. This application contains claims 9-14, 20-24, 27-54, 57, 60 and 61 are drawn to an invention nonelected with traverse in the reply filed on 11-27-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

It is noted that the original restriction requirement mailed 9-26-06 is a restriction among group I-XIII rather than an election of species.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated for the reasons set

forth in the preceding Official action mailed 4-23-08. Applicant's arguments filed 12-17-08 have been fully considered but they are not persuasive.

Applicants argue that the present invention relates to ablation of activity of the M2-2 protein, resulting in a phenotype of attenuation of replication and heighten sensitivity to interferon. Applicants do not need to describe mutations that provide for retention of M2-2 activity. The specification describes partial or complete deletion of the gene, introduction of stop codon or a frame-shift mutation into coding sequence, and alteration of the translation start signal as discussed on page 36, line 30 to page 37, line 13 (amendment, p. 14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-08. The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. The claims encompass a genus of various rHMPV strains and substrains having different nucleotide sequences. The specification only discloses the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2). HMPV appears to be a newly identified and classified virus in 2001. The claims encompass a genus of structural variants of SEQ ID No. 1 or 2, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of the variants that one skilled in the art can envision the nucleotide sequence of any other HMPV strain or substrain. No common structural attributes identify the members of the genus. It is apparent that applicants only have possession

of the nucleotide sequence of HMPV strain 83 and strain 75 but do NOT have possession of nucleotide sequence of any other HMPV strains or substrains. The claims also read on one or more attenuating modification comprising deleting or substituting the nucleotide sequence of M2-2 ORF of any HMPV that **reduces** or ablates expression. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The specification fails to provide structural features among the nucleotide sequences of various HMPV viruses that contribute to reduction of M2-2 expression and attenuated replication of the HMPV viruses. The biological function of the variant proteins was unpredictable at the time of the invention. The specification also fails to provide guidance for what and whether those variant proteins could result in the phenotypic change as recited in the claims. The nucleotide sequence of the disclosed M2-2 ORF is insufficient to describe the claimed recombinant HMPVs. This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed recombinant HMPVs and expression vector comprising said HMPVs.

4. Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant HMPV lacking M2-2 ORF as disclosed in the specification, wherein rHMPV lacking M2-2 ORF (ΔM2-2) replicates more than 10-fold less efficiently than wild type HMPV in LLC-MK2 cells and the ΔM2-2 mutant HMPV is more sensitive to interferon as compared to wild type rHMPV-GFP, does not reasonably provide enablement for any recombinant human metapneumovirus (rHMPV)

comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV, wherein said rHMPV results in the phenotypic change recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 4-23-08. Applicant's arguments filed 12-17-08 have been fully considered but they are not persuasive.

Applicants argue that M2-2 is a gene important for controlling the replication of HMPV and complete deletion of the M2-2 ORF results in an attenuated phenotype of the virus and a mutation that results in a decline in activity of the M2-2 ORF would also result in attenuation of viral replication. Applicants cite Examples 2, 3 and 5 and argue that the specification teaches how to make any mutation in the HMPV and how to test mutated viruses for a suitable degree of attenuation of replication (amendment, p. 14-15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-08. The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. The claims encompass various attenuated replication competent recombinant HMPVs having one or more attenuating modification comprising deleting or substituting the

nucleotide sequence of M2-2 ORF of any HMPV that **reduces** or ablates expression. The substitution or deletion could be one to several hundreds of nucleotides within various known and unknown HMPV viruses. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The specification fails to provide structural features among the nucleotide sequences of various HMPV viruses that contribute to reduction of M2-2 expression and attenuated replication of the HMPV viruses. There is no evidence of record that shows what nucleotides could be deleted or substituted with what nucleotides within M2-2 ORF such that an attenuated replication competent recombinant HMPV having reduced expression of M2-2 could be obtained. Although methods of making mutation and testing mutant virus are known in the art, what nucleotides could be deleted or substituted with what nucleotides within M2-2 ORF so as to result in reduced expression of M2-2 and an attenuated replication competent recombinant HMPV was unpredictable at the time of the invention. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the instant invention relates to ablation of activity of a protein and various ways to achieve it, and whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. Applicants further argue that disclosure of the complete genome of HMPV of the present application, together with description of tests for operability of the invention for its intended purpose, fulfills the requirement for enablement even in the face of a high degree of

unpredictability (amendment, p. 15-16). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-08 and the reasons set forth above. The claims encompass a **partial** or complete recombinant HMPV genome or antigenome comprising modified M2-2 gene, therefore, the nucleotide sequence of a complete genome of HMPV is not really necessary to make the claimed attenuated replication competent rHMPVs. Further, van den Hoogen et al. (2001) is the first to disclose the genomic sequence of HMPV. The complete genomic sequence of HMPV is disclosed on 4-15-02 as GenBank Accession No. AF371337 (van den Hoogen et al., 2001, p. 724, left column), which has 13350 nucleotides that is even longer than the 13335 nucleotides of HMPV disclosed in the instant invention. There is no evidence of record that shows what nucleotides could be deleted or substituted with what nucleotides within M2-2 ORF such that an attenuated replication competent recombinant HMPV having reduced expression of M2-2 could be obtained. Although methods of making mutation and testing mutant virus are known in the art, what nucleotides could be deleted or substituted with what nucleotides within M2-2 ORF so as to result in reduced expression of M2-2 and an attenuated replication competent recombinant HMPV was unpredictable at the time of the invention. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 55 and 56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS) and is repeated for the reasons set forth in the preceding Official action mailed 4-23-08. Applicant's arguments filed 12-17-08 have been fully considered but they are not persuasive.

Applicants cite Dr. Collins' declaration and argue that the biology of HMPV and RSV are different and effect of ablation of RSV M2-2 cannot predict the effect of ablation of HMPV M2-2. Van den Hoogen does not disclose complete sequence of the HMPV genome. The GenBank entry is incomplete for both genomic termini and neither the 5' nor 3' terminus of HMPV was mapped or sequenced by van den Hoogen. Applicant further argue that the leader sequence provided by van den Hoogen is incorrect at position 4 and the trailer sequence is incorrect at positions 4 and 5 (amendment, p. 16-20). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 4-23-08. Claims 55 and 56 are directed

to an expression vector comprising an operably linked transcriptional promoter, a partial or complete recombinant rHMPV genome or antigenome, and a transcriptional terminator, wherein the rHMPV genome or antigenome comprises one or more attenuating nucleotide modifications. Whether effect of ablation of RSV M2-2 can predict the effect of ablation of HMPV M2-2 or not is irrelevant because one of ordinary skill in the art only needs to prepare an expression vector rather than an attenuated replication competent HMPV. It would have been obvious for one of ordinary skill in the art at the time of the invention to construct an expression vector having a partial or complete HMPV genome or antigenome comprising one or more attenuating nucleotide modification of M2-2 as claimed because Bermingham teaches construction of such recombinant human RSV and van den Hoogen teaches the nucleotide sequence of HMPV, and both human RSV and HMPV are members of Pneumovirinae subfamily and clinical symptoms for human RSV and HMPV are largely similar. Since M2-2 ORFs are conserved in location but not in sequence and are thought to be involved in the control of the switch between virus RNA replication and transcription, it would be obvious for one of ordinary skill in the art to prepare the claimed expression vector with reasonable expectation of success in view of the teachings of Bermingham, Van den Hoogen (2001) and Van den Hoogen (2002). Van den Hoogen et al. (2001) is the first to disclose the genomic sequence of HMPV. The complete genomic sequence of HMPV is disclosed on 4-15-02 as GenBank Accession No. AF371337 (van den Hoogen et al., 2001, p. 724, left column), which has 13350 nucleotides that is even longer than the 13335 nucleotides of HMPV disclosed in the instant invention. It appears that van den Hoogen discloses the complete sequence of the HMPV genome. Examiner does not understand why applicants assert only partial genomic sequence was disclosed by van den Hoogen. Examiner is

confused as to what 5' and 3' terminus sequence, and leader and trailer sequences applicants discuss on page 19 of the amendment. Further, whether the sequence errors pointed out by applicants in the sequence disclosed by van den Hoogen is real an error or not remains to be seen. Whether the 5' and 3' terminus sequences and leader and trailer sequences are disclosed or are correct or not is irrelevant regarding the preparation of the claimed expression vector because van den Hoogen appears to disclose the complete sequence of HMPV genome and even if the sequence is not complete genomic sequence one of ordinary skill in the art would still be able to prepare the expression vector as claimed in view of the teachings of Bermingham, van den Hoogen (2001) and van den Hoogen (2002) with reasonable expectation of success.

Conclusion

No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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